

Crystal Structure of N^α -Di-*t*-Butoxycarbonyl L-Alanine

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The crystal structure of N^α -di-*t*-butoxycarbonyl L-alanine at 297 K has been determined by X-ray diffraction. The crystals are monoclinic with space group $P2_1$ and cell dimensions $a = 11.548(1)$, $b = 10.799(1)$, $c = 12.789(1)$ Å and $\beta = 90.291(8)^\circ$. The final R -value was 0.056. The molecules form hydrogen-bonded dimers. The molecular conformation is affected by a short non-bonded intramolecular oxygen–oxygen contact.

During the use of N^α -di-*t*-butoxycarbonyl amino acids (Boc₂-amino acids) in peptide synthesis, a decrease in reactivity, as compared to the corresponding Boc-amino acids, was observed, indicating the presence of a considerable steric hindrance.¹ In solution, Boc₂-amino acids could be linked to amino acid esters in high yields after prolonged reaction times. However, in competitive experiments, when Boc₂-amino acids and Boc-amino acids were simultaneously coupled to an amino acid Merrifield resin, only Boc₂-Gly coupled to any extent. The present investigation was carried out to gain knowledge of the structure of this type of compound. Boc₂-L-Ala was chosen as the model for several reasons. The compound was easy to crystallize, and the structures of both Boc-D-Ala and Boc-D,L-Ala have been published earlier,² giving the possibility of comparing the new derivative to chemically well studied compounds. As mentioned above, there was a difference in reactivity between Boc₂-Gly and the amino acid derivatives that carried side-chains, making glycine an exception and alanine a better model.

Experimental

Boc₂-L-Ala (C₁₃H₂₃NO₆, $M_r = 289.33$) was synthesized as described,³ and crystals were obtained by recrystallisation from a 1:3 mixture of diethyl ether and light petroleum.

X-Ray data: collection and reduction. A crystal of the title compound of dimensions $0.40 \times 0.35 \times 0.34$ mm was used for cell parameter determination and intensity data collection at 297 K. A Stoe four-circle diffractometer with graphite-monochromatized Mo $K\alpha$ radiation ($\lambda = 0.71073$ Å) was used for the diffraction experiment. Cell parameters were obtained from the least-squares fit to 20 observed 2θ -values in the range 20 – 25° . The dimen-

sions of the monoclinic unit cell are $a = 11.548(1)$, $b = 10.799(1)$, $c = 12.789(1)$ Å, $\beta = 90.291(8)^\circ$ and $V = 1594.8(4)$ Å³. There are four formula units in the unit cell. A total of 10269 reflexions were collected in an ω - 2θ step-scan mode with 60 steps of 0.015° in ω . Data were collected in the range $-16 \leq h \leq 16$, $-12 \leq k \leq 15$, $-17 \leq l \leq 0$ and $2 \leq 2\theta \leq 60^\circ$. After deleting space group extinguished reflexions, a data set of two unique units and a total of 9616 reflexions remained. Net intensities were derived with the profile analysis method of Lehman and Larsen.⁴ Five intensity test reflexions had been monitored every fourth hour. Intensities and their standard deviations were corrected for test reflexion variations by the method of McCandlish *et al.*⁵ An absorption correction for $D_c = 1.22$ Mg m⁻³ and $\mu = 0.0896$ mm⁻¹ gave transmission factors of 0.967–0.978. Lorenz and polarization factors were applied.

Solution and refinement of the structure. Diffraction symmetry and systematic extinctions indicated that the space group could be $P2_1$ or $P2_1/m$. Since the crystals were made from pure Boc₂-L-Ala, only the noncentrosymmetric spacegroup $P2_1$ was used for the calculations. The structure was solved with direct methods using the program MULTAN.⁶ There are two independent molecules in the asymmetric unit. All 40 non-hydrogen atoms could be identified among the 54 highest peaks in the first E -map. A set of 18 atoms in one molecule is related with the same set in the other molecule by a pseudo-mirror glide in the a -direction. The remaining four atoms, the oxygen atoms in the carboxyl groups, gave eight peaks in the E -map. These eight peaks correspond to the superposition of the L- and D-forms of the amino acid. By choosing the correct coordination around the asymmetric carbon atom it was possible to refine the heavy atom structure. After introduction of ADPs (anisotropic displacement parameters, previously called anisotropic thermal parameters), it was possible to locate all hydrogen atoms in a series of $\Delta\rho$ -calculations

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and least-squares refinements. Large mobility in the *t*-butyl methyl groups and high correlations due to the pseudo-symmetry gave poor convergence in the refinements. Introduction of anharmonic terms in the displacement parameters for six of the *t*-butyl methyl carbon atoms aided the convergence and the refinements could be completed. In the final cycle of refinement based on F^2 , including all 9616 reflexions, one scale factor, one isotropic extinction coefficient, 257 positional parameters, 240 anisotropic displacement parameters, 60 anharmonic displacement parameters and 46 isotropic displacement parameters were refined. The final values of these parameters are available from the authors on request.

The weights in the refinement were calculated from the standard deviation of each reflexion by the formula $w = [\sigma(F^2)]^{-2}$. No shifts were greater than 0.1σ , and the agreement factors were $R(F^2) = 0.050$, $\omega R(F^2) = 0.066$ and $S = 1.95$. The difference electron density calculated after the final refinement varied between -0.13 and 0.17 e \AA^{-3} . All computer programs used for the structure calculations have been described by Lundgren.⁷

Description of the structure and discussion

Fractional atomic coordinates and U_{eq} values for oxygens, nitrogens, carbons, and hydrogens H(45) and H(46) are given in Table 1, and the crystal packing is shown in Fig. 1. The structure consists of hydrogen-bonded dimers with some difference in conformation between the monomers. The carboxyl groups of the two molecules in the asymmetric unit are hydrogen-bonded to each other forming an almost planar ring (Fig. 2). The differences in C–O bond lengths in the carboxyl groups indicate that the hydrogen-bond system is ordered, with O(1) and O(2) as acceptors and O(3) and O(4) as donors of the hydrogen bonds. This is also consistent with the refined positions of the hydrogen atoms in the hydrogen bonds. The formation of dimers is common in carboxylic acid crystals, and the geometry of the hydrogen-bond system is in agreement with previous results.⁸

The molecules, with atom labelling and intramolecular bond lengths, are shown in Fig. 3, and the bond angles in Table 2.

Bond distances and angles in the two independent molecules agree well. The spread in C–C distances in the *t*-butyl groups should not be regarded as chemically significant, but rather as an indication of the difficulties exhibited by the refined model in describing the large torsional motion for these groups. The methyl groups of all four *t*-butyl groups are in a staggered position relative to their corresponding O–C bonds. All four *t*-butyl groups are, in a similar way, slightly distorted from regular tetrahedral geometry. A similar distortion is generally observed in all Boc-amino acids.⁹ The groups are tilted away from the ester carbonyl oxygen, which leads to a decrease in the C–C–O bond angle involving the methyl carbon *trans* to the C–O ester bond. These bond angles

Table 1. Atomic coordinates ($\times 10^4$, for hydrogen atoms $\times 10^3$) and U_{eq} values (in $\text{\AA}^2 \times 10^2$).^a

Atom	X	Y	Z	$U_{\text{eq}}/U_{\text{iso}}$
O(1)	4383(1)	7005	6597(1)	5.1
O(2)	7278(1)	6405(1)	6587(1)	5.3
O(3)	5302(1)	5197(1)	6624(1)	5.2
O(4)	6434(1)	8238(1)	6812(1)	5.8
O(5)	4264(1)	3224(1)	8677(1)	5.0
O(6)	9352(1)	9969(1)	8660(1)	5.1
O(7)	2933(1)	2847(1)	5743(1)	5.7
O(8)	8467(1)	10582(1)	5685(1)	6.6
O(9)	3719(1)	5221(1)	8523(1)	4.0
O(10)	8676(1)	8022(1)	8438(1)	4.1
O(11)	3088(1)	1919(1)	7299(1)	4.8
O(12)	8192(1)	11347(1)	7286(1)	5.0
N(1)	3376(1)	3981(1)	7176(1)	3.7
N(2)	8571(1)	9317(1)	7094(1)	3.7
C(1)	4374(1)	5862(2)	6608(1)	4.1
C(2)	7323(1)	7542(1)	6637(1)	4.0
C(3)	3264(1)	5124(2)	6557(1)	3.9
C(4)	8432(1)	8221(2)	6405(1)	3.9
C(5)	2185(1)	5873(2)	6790(1)	5.0
C(6)	9492(1)	7400(2)	6346(1)	5.3
C(7)	3842(1)	4055(2)	8199(1)	3.8
C(8)	8908(1)	9174(2)	8143(1)	3.8
C(9)	3126(1)	2871(2)	6663(1)	4.1
C(10)	8418(1)	10473(2)	6611(1)	4.3
C(11)	4271(1)	5710(2)	9492(1)	4.3
C(12)	9218(1)	7487(2)	9400(1)	4.4
C(13)	2897(2)	657(2)	6897(1)	4.8
C(14)	7943(2)	12630(2)	6936(1)	5.4
C(15)	5574(1)	5577(2)	9409(1)	5.5
C(16)	10517(1)	7605(2)	9350(2)	5.7
C(17)	3787(2)	5072(3)	10438(1)	6.0
C(18)	8730(2)	8057(3)	10358(1)	6.8
C(19)	3919(2)	7048(2)	9453(2)	6.0
C(20)	8880(2)	6128(2)	9308(2)	6.4
C(21)	2932(8)	-102(5)	7868(4)	7.6
C(22)	7717(8)	13276(6)	7935(4)	7.6
C(23)	1705(7)	589(7)	6418(8)	8.9
C(24)	6838(12)	12547(9)	6301(8)	11.0
C(25)	3897(7)	320(6)	6183(6)	9.2
C(26)	8970(12)	13130(7)	6420(10)	10.7
H(45)	405(2)	63(3)	341(2)	12.5
H(46)	428(3)	288(3)	323(2)	15.8

^a The estimated standard deviations are given in parentheses. $U_{\text{eq}} = (u_1 u_2 u_3)^{2/3}$.

are in the range 101.5 – 102.4° . The C–C–C bond angle involving the other two methyl groups in the *t*-butyl group is increased to the range 112.5 – 117.6° . All *t*-butyl groups are *trans* with respect to the nitrogen atoms, and the C–O–C ester bond angle is in the range 120.7 – 123.3° , as also observed in Boc-D-Ala and Boc-D,L-Ala.²

The coordination around the nitrogen atom is almost planar in both molecules (Table 3). The C(3)–N(1) and C(4)–N(2) bonds [$1.472(2)$ and $1.487(2) \text{ \AA}$] are slightly longer than the corresponding bond in Boc-D-Ala (1.449 \AA). The bond lengths between C(7), C(8), C(9) and C(10) and the respective nitrogens are 0.051 – 0.069 \AA longer than in Boc-D-Ala.²

The torsion angles (ω_{ij}) around the N–C bonds

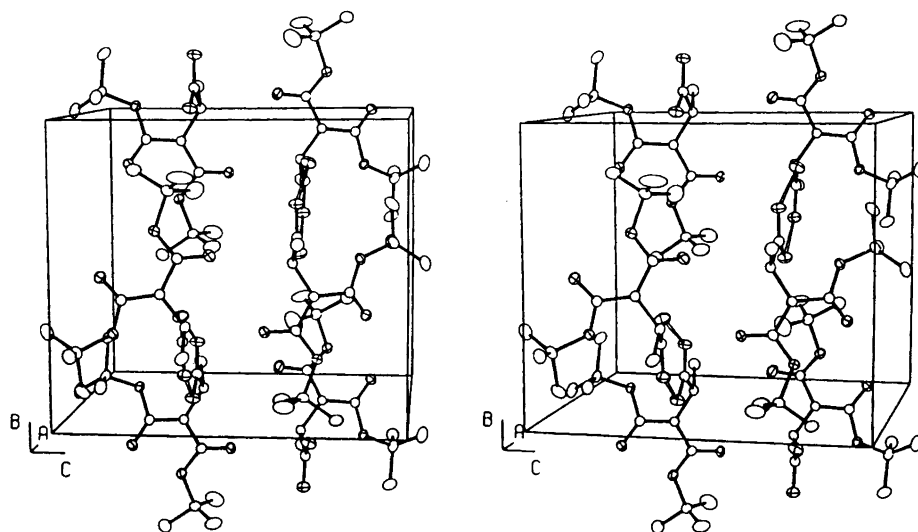


Fig. 1. Stereoscopic drawing of the structure viewed along *a*. Covalent bonds are filled, hydrogen bonds are open. Atoms are scaled to include 11% probability. Figures are drawn with the program ORTEP II.¹⁰

(Table 4) show some deviations from expected values. For a tertiary nitrogen one would expect a *cis* urethane bond,⁹ but in the present structure, both molecules have one *cis* and one *trans* urethane bond. The deviations from the ideal values of the torsion angles (0 and 180°) are usually less than 10°, but in the present structure are in the range 9–21°. The combination of one *cis* and one *trans* urethane bond will place the bulky *t*-butyl groups at a

large distance from each other, but at the expense of the short non-bonded oxygen–oxygen contacts O(5)–O(11), 2.629(2) Å, and O(6)–O(12), 2.660(2) Å. The deviation from ideal values for the torsional angles will increase these oxygen–oxygen distances. One can also see that the bond angles around C(7), C(8), C(9) and C(10) are distorted so as to increase these oxygen–oxygen distances.

The bonding angles around the α -carbons C(3) and

Table 2. Bond angles (in °).

O(1)–C(1)–O(3)	123.4(1)	N(1)–C(3)–C(1)	110.3(1)
O(1)–C(1)–C(3)	122.2(1)	N(1)–C(3)–C(5)	114.3(1)
O(2)–C(2)–O(4)	123.7(1)	N(2)–C(4)–C(2)	111.1(1)
O(2)–C(2)–C(4)	120.8(1)	N(2)–C(4)–C(6)	114.3(1)
O(3)–C(1)–C(3)	114.3(1)	C(7)–O(9)–C(11)	123.3(1)
O(4)–C(2)–C(4)	115.3(2)	C(8)–O(10)–C(12)	120.7(1)
O(5)–C(7)–O(9)	126.7(1)	C(9)–O(11)–C(13)	120.9(1)
O(5)–C(7)–N(1)	125.9(2)	C(10)–O(12)–C(14)	121.0(1)
O(6)–C(8)–O(10)	127.0(1)	C(3)–N(1)–C(7)	118.9(1)
O(6)–C(8)–N(2)	124.4(2)	C(3)–N(1)–C(9)	116.7(1)
O(7)–C(9)–O(11)	125.8(2)	C(4)–N(2)–C(8)	120.6(1)
O(7)–C(9)–N(1)	121.2(2)	C(4)–N(2)–C(10)	115.8(1)
O(8)–C(10)–O(12)	126.6(2)	C(7)–N(1)–C(9)	124.1(1)
O(8)–C(10)–N(2)	121.2(2)	C(8)–N(2)–C(10)	123.5(1)
O(9)–C(7)–N(1)	107.5(1)	C(1)–C(3)–C(5)	114.1(1)
O(9)–C(11)–C(15)	109.2(1)	C(2)–C(4)–C(6)	114.4(2)
O(9)–C(11)–C(17)	110.4(1)	C(15)–C(11)–C(17)	112.8(2)
O(9)–C(11)–C(19)	101.5(1)	C(15)–C(11)–C(19)	110.9(2)
O(10)–C(8)–N(2)	108.6(1)	C(16)–C(12)–C(18)	112.5(2)
O(10)–C(12)–C(16)	110.2(1)	C(16)–C(12)–C(20)	109.5(2)
O(10)–C(12)–C(18)	111.1(2)	C(17)–C(11)–C(19)	111.5(2)
O(10)–C(12)–C(20)	101.6(1)	C(18)–C(12)–C(20)	111.4(2)
O(11)–C(9)–N(1)	112.9(1)	C(21)–C(13)–C(23)	109.5(5)
O(11)–C(13)–C(21)	102.4(2)	C(21)–C(13)–C(25)	110.6(4)
O(11)–C(13)–C(23)	108.8(3)	C(22)–C(14)–C(24)	109.8(6)
O(11)–C(13)–C(25)	108.6(3)	C(22)–C(14)–C(26)	111.2(6)
O(12)–C(10)–N(2)	112.2(1)	C(23)–C(13)–C(25)	116.0(5)
O(12)–C(14)–C(22)	102.4(2)	C(24)–C(14)–C(26)	117.6(7)
O(12)–C(14)–C(24)	105.6(4)	O(2)–H(45)–O(3)	176(3)
O(12)–C(14)–C(26)	108.9(4)	O(1)–H(46)–O(4)	173(3)

Table 3. Selected least-square planes.

Plane	Atoms included in plane	Interplanar angles/°				Distance from plane/Å
		1	2	3	4	
1	C(3), C(7), C(9)					N(1) 0.050(1)
2	C(4), C(8), C(10)					N(2) 0.029(1)
3	C(7), O(5), O(9)	3	18.0			
4	C(8), O(6), O(10)	4		19.5		
5	C(9), O(7), O(11)	5	11.2		26.8	
6	C(10), O(8), O(12)	6		21.1		37.2

Table 4. Selected torsion angles (in °).

N(1)-C(3)-C(1)-O(3)	36.3(1)
N(2)-C(4)-C(2)-O(4)	41.0(2)
C(7)-N(1)-C(3)-C(1)	47.4(2)
C(8)-N(2)-C(4)-C(2)	76.0(2)
C(9)-N(1)-C(3)-C(1)	-125.8(1)
C(10)-N(2)-C(4)-C(2)	-107.9(1)
O(9)-C(7)-N(1)-C(3)	21.3(2) ^a
O(10)-C(8)-N(2)-C(4)	-20.9(2) ^b
O(11)-C(9)-N(1)-C(3)	-171.0(1) ^c
O(12)-C(10)-N(2)-C(4)	159.9(1) ^d

^a ω_{11} , ^b ω_{21} , ^c ω_{12} , ^d ω_{22} .

C(4) are also distorted. For a tetrahedral α -carbon, the expected sum of bond angles not involving hydrogen would be ca. 330° . This value is found in Boc-D-Ala and Boc-D,L-Ala,² but the value for the present structure is ca. 338° in both molecules. The hydrogen atoms H(1) and H(2) bonded to the α -carbons are involved in hydrogen-bond like interactions with O(7) and O(8), respectively, with $H \cdots O$ distances of 2.24(2) and 2.19(2) Å. It is thus obvious that the α -carbon is affected sterically and/or electronically by a second Boc-substituent on the nitrogen, and this might explain the reduced reactivity of Boc₂-L-Ala.

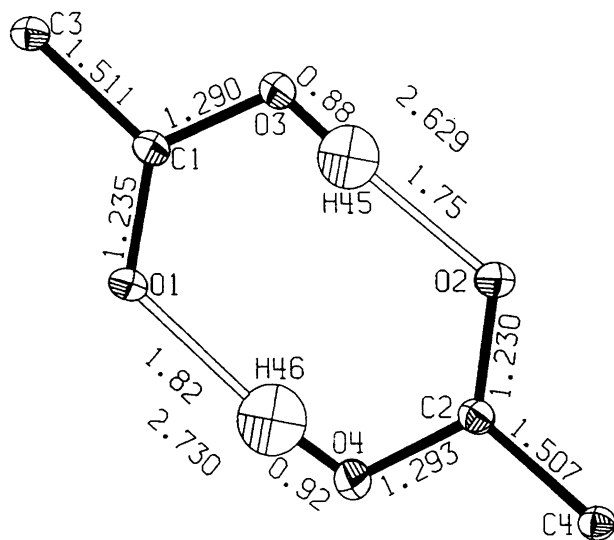
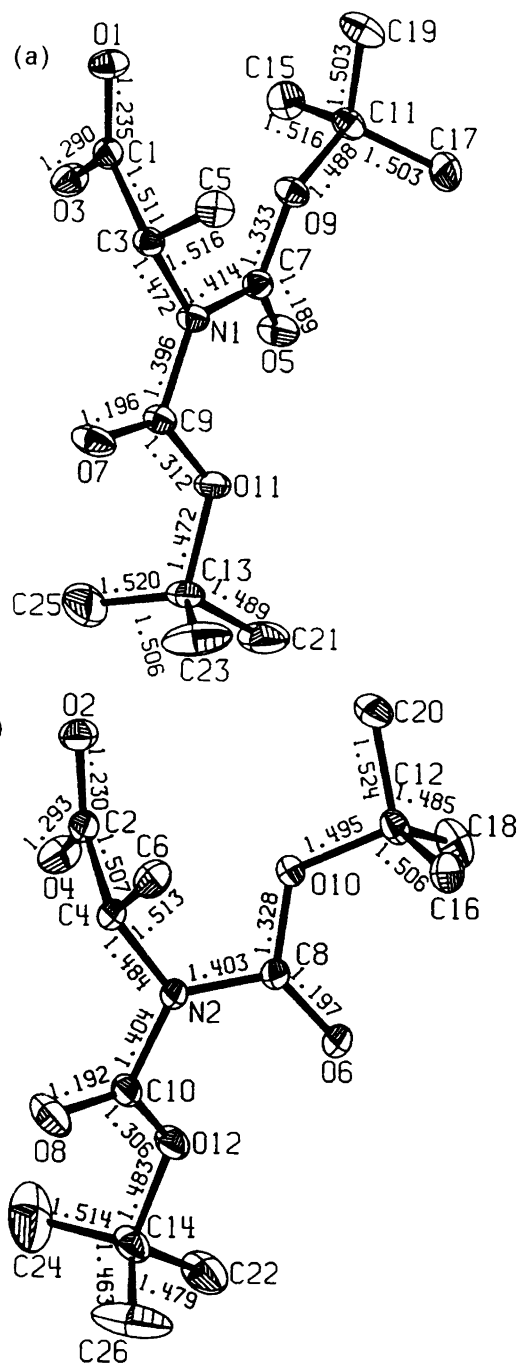


Fig. 2. The hydrogen-bonded carboxyl group.

Fig. 3. The geometries of the two independent molecules. $\sigma(d) < 0.002$ Å except for *t*-butyl groups, where $\sigma(d) < 0.013$ Å.

The structure derived here is well in accordance with the observed low reactivity due to the bulky protecting groups. The space around the nitrogen is crowded and forces the ester carbonyls to take positions with torsion angles deviating from the normal values close to 0 or 180°.

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